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10/645,451	08/21/2003	Joseph L. Bryant	4115-150 CIP DIV	7909
23448 7590 07/11/2007 INTELLECTUAL PROPERTY / TECHNOLOGY LAW PO BOX 14329			· EXAMINER	
			NOBLE, MARCIA STEPHENS	
RESEARCH T	H TRIANGLE PARK, NC 27709		ART UNIT	PAPER NUMBER
			1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

	Application No.	Applicant(a)				
	Application No.	Applicant(s)				
	10/645,451	BRYANT ET AL.				
Office Action Summary	Examiner	Art Unit				
	Marcia S. Noble	1632				
The MAILING DATE of this communication app Period for Reply	ears on the cover sheet with the c	orrespondence address				
A SHORTENED STATUTORY PERIOD FOR REPLY WHICHEVER IS LONGER, FROM THE MAILING DA - Extensions of time may be available under the provisions of 37 CFR 1.13 after SIX (6) MONTHS from the mailing date of this communication. - If NO period for reply is specified above, the maximum statutory period w. - Failure to reply within the set or extended period for reply will, by statute, Any reply received by the Office later than three months after the mailing earned patent term adjustment. See 37 CFR 1.704(b).	ATE OF THIS COMMUNICATION 36(a). In no event, however, may a reply be tim vill apply and will expire SIX (6) MONTHS from to cause the application to become ABANDONE	l. ely filed the mailing date of this communication. O (35 U.S.C. § 133).				
Status		·				
1) Responsive to communication(s) filed on 23 Ap	Responsive to communication(s) filed on 23 April 2007.					
2a) This action is FINAL . 2b) ⊠ This	This action is FINAL . 2b) ☑ This action is non-final.					
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closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11, 453 O.G. 213.						
Disposition of Claims						
4) ⊠ Claim(s) 1-21 is/are pending in the application. 4a) Of the above claim(s) 12-21 is/are withdraw 5) □ Claim(s) is/are allowed. 6) ⊠ Claim(s) 1-11 is/are rejected. 7) □ Claim(s) is/are objected to. 8) □ Claim(s) are subject to restriction and/or	n from consideration.					
Application Papers						
9) The specification is objected to by the Examiner 10) The drawing(s) filed on is/are: a) access Applicant may not request that any objection to the of Replacement drawing sheet(s) including the correct of the oath or declaration is objected to by the Examiner	epted or b) objected to by the Eddrawing(s) be held in abeyance. See ion is required if the drawing(s) is obj	e 37 CFR 1.85(a). ected to. See 37 CFR 1.121(d).				
Priority under 35 U.S.C. § 119						
 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f). a) All b) Some * c) None of: 1. Certified copies of the priority documents have been received. 2. Certified copies of the priority documents have been received in Application No. 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)). * See the attached detailed Office action for a list of the certified copies not received. 						
Attachment(s) 1) Notice of References Cited (PTO-892) 2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 3) Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date	4) Interview Summary Paper No(s)/Mail Da 5) Notice of Informal P 6) Other:	ate				

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DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/23/2007 has been entered.

Status of Claims

2. Claims 1-21 are pending. Claims 1, 5, 11, and 12 are amended by Applicant's response, filed 2/13/2007.

Election/Restrictions

3. Claims 12-21 were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4/7/2006.

Claims 1-11 are under consideration.

Priority

4. In the previous Office Actions, the instant application was not given the effective filing of the prior-filed application, Application No. 09/058,113, filed 4/9/1998, because it failed to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

This denial to the priority documents has been reconsidered. The priority documents contemplate the instantly claimed transgenic rats in broad terms and therefore the benefit of priority to the earlier filing date will be granted.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement

5. The rejection of claims 1-11, under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic rat, whose genome comprises a transgene encoding a portion of or a full length CD4 protein that binds to gp120 and CCR5 or CXCR4, if present, and mediates entry of HIV and wherein the CD4 transgene contains a PMBC specific promoter resulting in expression of the CD4 on PMBCs of the transgenic rat and wherein the transgenic rat further comprises a second transgene in its genome encoding a CCR5 or CXCR4 wherein the second transgene comprises a PMBC specific promoter resulting in the expression of CCR5 or CXCR4 on PMBCs,

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does not reasonably provide enablement for a transgenic rat, whose genome comprises at least one copy of a transgene encoding at least a portion of a CD4 protein sufficient for binding to gp120, wherein CD4 encoded by the transgene is expressed on PMBCs of the transgenic rat and wherein the genome further comprises a transgene encoding for at least a portion of CCR5 or a gene encoding CXCR4, as set forth on pages 4-6 in the Office Action, mailed 5/31/2006, is withdrawn.

After consideration of the amended claims and argument provided by applicant, the instant reject is being withdrawn and a new enablement rejection is being applied as set forth below.

Enablement

6. Claims 1-11are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a transgenic rat, whose genome comprises a transgene encoding at least a portion of a CD4 protein that bind gp120 operably linked to a PBMC-specific promoter sufficient for expression of the transgene, wherein CD4 encoded by the transgene is expressed on PBMC of the transgenic rat and wherein the transgenic rat is adapted to model human HIV infection (claim 1). Narrowing embodiments specify that the transgenic rat further comprise a transgene encoding a portion of CCR5 (claim

2), that the CD4 be a human CD4 (claim 3), and that the CD4 be a full length CD4 (claim 4). Narrowing embodiments specify that the CD4 and the CCR5 in the transgenic mouse are capable of mediating entry of the HIV (claim 5) Narrowing embodiments encompass cell from the transgenic rat (claims 6 and 7), more specifically germ cells (claim 8), somatic cells (claim 9), or an egg (claim 10). The claims are also drawn to transgenic rat, whose genome comprises a gene encoding a CXCR4 and a transgene encoding at least a portion of a CD4 protein that bind gp120 operably linked to a PBMC-specific promoter sufficient for expression of the transgene, wherein the CXCR4 encoded by the gene and CD4 encoded by the transgene is expressed on PBMC of the transgenic rat and wherein the transgenic rat is adapted to model human HIV infection (claim 11)

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The instant specification discloses the production of transgenic rats comprising a transgene encoding the full length human CD4 protein that is operabley linked to the lymphocyte specific protein tyrosine p56 lck promoter (Example 11, page 50, par 1). The specification also provides evidence that the PBMCs of the transgenic rat express the human CD4 transgene (p. 20, par 3 and Figure 3). The specification also discloses prophetic methods by which the infectivity of the PBMCs of the transgenic rat with HIV virus can be tested (p. 51, lines 3-22). The specification also teaches that the mechanism by which HIV-1 infects human PBMC is by binding of the CD4 protein with the gp120 of the HIV virus and allowing the HIV-1 to interact with the co-receptors CC5 or CXCR4 (p. 4, par 2 and par bridging page 19-20). The specification also prophetically teaches that transgenic non-human animals can be made with infectious HIV transgenes, alone or in conjunction with a transgene encoding a CD4 and/or an HIV co-receptor transgene (e.g.-CCR5 or CXCR4; p. 27, lines 21-25) and that double transgenic rats comprising an HIC and CD4 transgene can be made by crossing HIV-1 transgenic rats and CD4 transgenic rats (example 12, p. 51, lines 25-26).

First, with regard to a CD4 transgenic rat, the specification teaches that although human CD4 is essential for HIV infection it is not sufficient to mediate HIV infection on

its own (p. 4, par 2). The art teaches that human expression of CD4 in transgenic mice does not confer sensitivity to HIV-1 infection (p.1145, par bridging col 1 and 2 of Sawada et al. J Exp Med 178(9):1439-1449, May 4, 1998; of record). Therefore, since the art and the specification suggest that CD4 needs additional cofactors such as CXCR4 or CCR5 to mediate HIV-1 infection in a human or in a transgenic rodent, an artisan would not know how to use a transgenic rat solely expressing CD4 as to model HIV infection as the claims encompass. Therefore, the instant invention is not enabled for a CD4 transgenic rat wherein the transgenic rat is adapted to model HIV infection.

Second, the instant claims are directed to CD4 transgenic rat, a CD4/CCR5 transgenic rat, and a CD4/CXCR4 transgenic rat that are adapted to model human HIV infection (claim 1) or capable of mediating entry of HIV (claim 3 and 11), however, the specification only prophetically teaches the making these transgenic rats. While the methods of making a transgenic rat were established at the time of filing, the phenotype that would result in such a transgenic rat is unpredictable in the art.

Mullins et al teaches that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes (Mullins et al Hypertension 22:631, col 1, par 1, lines 14-17, 1993). The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression (e.g. specific promoters, presence or absence of introns, etc. (Houdebine J. Biotech 34:281, 1994). Mullins et al disclose that "the use of non-murine species for transgenesis will continue to reflect the

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suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to the another."

(Mullins et al. J Clin Invest 98:S39 summary, 1996). Therefore, overall, the art teaches that the production of one species of transgenic animal with a given phenotype does not predictably transfer to the production of transgenic animal of another species.

In the instant case, the invention claims a transgenic rat that is adapted to model HIV infection and is capable of mediating entry of HIV. The art teaches a transgenic mouse co-expressing CD4 and CCR5 or CD4 and CXCR4 in PBMCs. It also teaches that expression of CD4 and CCR5 or CD5 and CXCR4 by the PBMCs of these transgenic mouse mediate entry of HIV-1 into the PBMC (see pages 1445, col 1 of Sawada et al and p. 1460 of Browning et al; of record). However, the specification only prophetically teaches the production of this transgenic rat. Therefore, because the art teaches that obtaining a given phenotype in a new line of transgenic species is unpredictable, an artisan would not know how to produce a transgenic rat with that mediates entry of HIV-1 into PBMC as claimed because the specification does not provide teaches to overcome the unpredictabilities described in the art.

Third, the art teaches that transgenic mice expressing CD4 and CCR5 or CD4 and CXCR4 results in HIV-1 infection of PBMCs from the transgenic mice to some extent (see page 1445, col 1 of Sawada et al and page 1460 of Browning et al. PNAS 94:14637-14641, 1997; of record). However, Sawada et al teaches that transgenic mice coexpressing of CD4 and hCXCR4 had significantly lower levels of p24 antigen than that produced by human PBMC following infection with HIV-1 and that this

suggests that additional factors are required to efficiently replicate viruses in mouse lymphocytes (p. 1445, col 1). Browning et al state that the coexpression of CD4 and CCR5 in T cells of transgenic mice permitted in vivo HIV-1 infection of the T-cells from these transgenic mice albeit at a much lower level than in human T cells (p. 146410, col 2. par 1). Browning et al further state (p. 14640, col 2, last par), "Taken together these results suggest that although expression of human CD4 and a chemokine receptor such as CCR5 may be sufficient to permit entry of HIV-1 into mouse cells, the combined effect of impairment in other stated of HIV replication in mouse cell may prevent the development of sustained infection in these human CD4/CCR5 transgenic mice. Therefore, the presence of additional blocks that prevent efficient HIV replication in mouse cells complicates the use of transgenic mice to investigate the immunopathology of HIV-1 infection." Therefore, the art suggest that are additional factors unique to human HIV-1 infection that are not being accounted for in the art recognized transgenic mice. Therefore, because the art suggests that more factors need to be present in transgenic animal models than CD4 and CCR5 or CXCR4 to model human HIV infection, the sole co-expression of CD4 and CCR5 or CD4 and CCR5 may not provide a sufficient model human HIV infection as claimed. Neither the art nor the specification provides teaching of additional cofactors that may be needed in the making of the CD4/CCR5 transgenic mouse that will model human HIV infection. Therefore, since the art teaches that CD4/CXCR4 or CD4/CCR5 transgenic animals require additional factors to model human HIV infection and neither the art nor the specification teach the factors needed to facilitate a phenotype that would model human HIV, an artisan would

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not know how to make a CD4/CXCR4 or CD4/CCR5 transgenic rat that models human HIV as claimed.

Fourth, the instant claims encompass a CD4 transgenic rat, a CD4/CCR5 transgenic rat, and a CD4/CXCR4 comprising a portion of the CD4 protein that binds gp120 but can not mediate entry of an HIV virus. The art teaches that certain regions and interaction sites on the CD4 and gp120 are necessary for CD4 to bind to gp120 an mediate HIV infection (Farrar et al Crit Rev Immunol 8(4):315, abstract, 1988). Reeves and Doms (J Gen Virol 83:1253-1265, 2002) teach that HIV-1 binding to these regions of CD4 induces a conformational change in HIV-1 tat is important in coreceptor binding and cell entry (p. 1256, par bridging col 1 and 2). However, the claims encompass portions of the CD4 that would not encompass the regions that bind but not mediate HIV infection. Therefore, an artisan would not know how to use a transgenic rat comprising portion of the CD4 that binds gp120 and does not mediate HIV infection as a model for human HIV infection as claimed because such a portion would not mediate HIV infection. Therefore, such embodiments are not enabled by the specification.

Fifth, the instant claims encompass transgenic rats that express CD4 that mediates entry of any strain of HIV virus into PBMCs. The specification teaches transgenic rats that can be infected with HIV-1. The art teaches that while HIV infections are mostly due to HIV type 1 strains, HIV-2 represents a significant minority of all HIV infections (Reeves and Doms, p. 1253, col 1, par 1), suggesting that at least 2 forms of HIV virus exist. Reeves and Doms teach that the most striking difference between HIV-1 and HIV-2 is that, while HIV-1 infection most commonly requires both

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CD4 and a coreceptor, many primary HIV-2 isolates exhibit CD4 independent infection (p. 1257, col 2, 1st full par). They also teach that some HIV-2 strains use coreceptors not utilized by HIV-1 (p. 1256, col 2) and are able to infect PBMCs independently of either CXCR4 or CCR5 (p. 1257, col 1, lines 1-2). Therefore, because the specification only teaches HIV-1 and the art suggests that other strains of HIV exist and utilize other mechanism of infections other that CD4 and CXCR4 or CCR5, an artisan would not know how to mediate entry of any other HIV virus into PBMC of the transgenic rat, other than HIV-1.

In summary, the instantly claimed transgenic rat lacks enablement because the state of the art of producing given phenotype in a new transgenic animal line is unpredictable. Since the specification does provide specific guidance as to overcome these unpredictabilities, the artisan would not know how to make a transgenic rat with the phenotype of modeling human HIV infection. Furthermore, the art suggest even the transgenic models expressing CD4 solely or coexpressing CD4 and CXCR4 or CCR5 do not provide models of human HIV infection established in the art. Therefore, it is unclear that the instantly claimed transgenic rat solely expressing CD4 or coexpressing CD4 and CXCR4 or CCR5 will be a model for human HIV as claimed. Therefore, the instant invention is not enabled because of the unpredictabilities and the disclosure of unknown factors modulating HIV infection and because the specification lack specific guidance to overcome the unpredictabilities and unknown factors in the art.

Written Description

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7. Claim(s) 1-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is drawn a transgenic rat comprising a transgene encoding a portion of a CD4 protein and a portion of CCR5.

When the claims are analyzed in light of the specification, the instant invention encompasses a portion of a CD4 protein and a portion of CCR5. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. While the specification mentions prophetically a portion of a CD4 protein and a portion of CCR5, the specification fails to disclose any portion of a CD4 protein or any portion of a CCR5 other than full length CD4 and full length CCR5 themselves. Therefore because the specification only discloses one species for each genus, a full length CD4 protein and a full length CCR5, the specification does not teach the complete structure of a representative number of species of the claimed genus that comprises a portion of a CD4 protein and a portion of CCR5.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant characteristics, specified features and functional attributes that would distinguish different members of the claimed genus. The specification discloses that CD4 binds gp120 and, along with it coreceptors, mediates

the entry of an HIV virus into PBMCs (p. 5, par 2). However, this does not specifically disclose any special identifying features/characteristics that would distinguish the species of the genus comprising a portion of a CD4 protein and a portion of CCR5. Therefore, a representative number of species have not been sufficiently described by other relevant characteristics, specified features and functional attributes in the specification as required by the written description requirement.

In conclusion, given the breadth of the genus, species have not been sufficiently described by other relevant characteristics, specified features and functional attributes, and the limited number of examples provided, and given that no specific identifying features/characteristic of species of the genus, were provided, the written description requirement disclosing the complete structure of genus comprising a portion of a CD4 protein and a portion of CCR5 has not been met. Furthermore, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of the genus comprising a portion of a CD4 protein and a portion of CCR5, at the time the application was filed.

New Matter

8. The rejection of claim 5, under 35 U.S.C. 112, first paragraph, as containing subject matter that would be considered new matter, is withdrawn.

Claim 5 recited, "wherein the at least a portion of a CD4 protein and the at least a portion of CCR5 encoded by the transgene.", which was deemed as new matter. The

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recent amendments to the claims no longer contain this recitation. Therefore, the rejection is most and therefore withdrawn.

However, the instant amendments to the claims also introduce new matter that necessitates the following rejection:

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Amended claim 1 recites "wherein the transgenic rat is adapted to model human HIV infection". The specification provides no literal support for this recitation. Applicant suggests that this new recitation is supported by the specification on page 5, lines 19-23. However, this passages of the specification teaches non-human transgenic models for lentiviral infection and development of diseases. Applicant also suggests that pages 19-23 support this recitation. However, pages 19-23 of the specification teach non-infectious transgenic animal models. Neither of these references provide teachings on how the claimed transgenic rat can be "adapted to model human HIV infection", therefore providing no figurative support for the breadth of this recitation.

Claim Rejections - 35 USC § 112, 2nd Paragraph

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The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. The rejection of claim 5, under 35 U.S.C. 112, second paragraph, as being indefinite in its recitation, "the transgene", is withdrawn.

Applicant amended the claims to now recite "the respective transgene", which clarifies the claim. Therefore the rejection is withdrawn.

However, the amendments to the claims introduce the following 112, second paragraph indefinite issues:

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Amended claims 1 and 11 recite "wherein the transgenic rat is adapted to model HIV infection". The metes and bounds of this recitation are indefinite because it is unclear how the transgenic rat is "adapted". The breadth of this recitation suggest that something additional needs to be done to the transgenic rat. However, the claims does not suggest what additional measures are needed or how the rat is to be "adapted". Furthermore, it is not clear from this recitation if serves as a functional limitation to the transgenic mouse or if it is an intended use.

Claims 2-10 are dependent on claim 1. Therefore, these dependent claims are indefinite.

Claim 5 recites "capable of mediating entry of HIV". The metes and bounds of this recitation are considered indefinite because the claim does not specify into what HIV is entering.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. The rejection of claims 1-11, under 35 U.S.C. 102(e) as being anticipated by Goldsmith et al (US Pat # 6,372,956 B1 4/16/2002; filing date 12/23/1999), is withdrawn.

Applicant traversed this rejection on the grounds that Goldsmith et al is not available as prior art because Goldsmith et al was filed on 12/23/1999 and the instant application is entitled to the priority date of 4/9/1998. Applicant's arguments are found persuasive and therefore the rejection is withdrawn.

11. No claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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